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THE USE OF ADRENAL SUBSTANCE
IN THE TREATMENT OF ASTHMA



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The experience I have to submit in the use of adrenal substance in this particular connection, is of but little importance, except as a link in a chain of studies.

The synthesis of disease—i. e., the manner in which syndrome groups are built up, and the reason of their association—is beginning to attract the attention of students who recognize that pathology is something more than morbid anatomy or bacteriology.

That wonderful system of compensations found throughout all Nature, the balanced action of contending forces producing mobile or stable equilibrium, and the motion that takes place in the direction of an inferior force, are not merely problems of physics, but also of biology, and of that special branch of biology which deals with the disturbances we call disease. The disruption of a planet, the aberration of a comet from its calculated orbit, may differ in magnitude from the destruction of an animal cell or the aberrant action of the heart and vessels, but essentially the same forces are at work. Provocatives in such disturbances are often forces of the en-

vironment, but sometimes the disturbing elements arise within the animal organism itself. Often the nature, and nearly always the order—for in Nature there is always order in disorder—of succession of these disturbances depends on the inherent properties of the organism attacked rather than on the attacking agent—be this microbial, chemical, or less tangible than either.

Within the human economy, a constant struggle of opposing activities—or perhaps it would be more accurate to say tendencies to action—results in orderly growth, development and function. The agents of these activities or tendencies are cells and their products. Deficiency or excess may lead directly to disorder or render order so unstable that it is easily overthrown by slight addition to the forces acting in some special direction.

We have not yet learned to realize the large part that the activities of the blood-vessels may take in determining symptomatology and lesions. A and B may both be exposed to the same storm, and the same incidence of pneumococci, yet A may escape and B suffer with lobar pneumonia. Why? Possibly, even probably, because B's vascular tone is more readily overthrown than A's, because the branches of his bronchial arteries are through permanent or temporary relations of vasomotor control, more readily paralyzed, permitting congestion to occur, and favorable culture conditions for the cocci to be established. But the same instability of vascular tone which, under certain conditions, leads to the development of pneumonia may, in other degrees and under other conditions of internal metabolism and of incidence of external forces, lead to other morbid phenomena, perhaps to Graves' disease; or will modify the symptomatology of visceral diseases or infectious fevers; or will be manifest in certain so-called idiosyncrasies to drugs or articles of diet. Thus a varied and apparently unrelated semeiology may be correlated with some structural, functional, or metabolic condition peculiar to the individual or,

more frequently, to classes of men; and these peculiarities may be acquired or congenital.

On the other hand, a certain symptom-complex, or symptoms-complex closely similar, may arise in different individuals, not only from different causes but even by apparently opposed mechanisms. Thus we can distinguish between two varieties of hemicrania, the one due to vascular spasm—anemic migraine—the other to vascular paresis—congestive migraine; the syndrome accordingly being relieved by nitrites and aggravated by adrenal substance, if spasmodic; or aggravated by nitrites and relieved by adrenal substance, if paretic.

Similarly I look on asthma, not as a definite nosologic entity, but as a morbid condition symptomatic in its nature and associated with various and varying pathologic processes and physical states. Every form of dyspnea, however, can not properly be called asthmatic, even those forms that by common consent have come to be designated as cardiac asthma and renal asthma; and while the former is sometimes susceptible of relief through the action of adrenal substance on the heart and vessels, I shall not in this paper refer to such cases.

Without restricting the term asthma, as is the tendency of most modern authors, to the typical paroxysm of dyspnea, arising suddenly and terminating with equal suddenness, it is, nevertheless, distinctly a paroxysmal disorder, arising independently of gross lesions of the circulatory, respiratory or excretory systems; although it may be associated with any or all of these, and be the more readily provoked through such association.

The disputes over its pathology are probably due to one-sided studies of one or another variety. Basing my opinion purely on clinical studies, as the question could scarcely be decided post-mortem, I have no doubt that in certain cases of asthma the immediate mechanism of the paroxysm is bronchial spasm, not only muscular but also frequently vascular; though perhaps in many cases

of vascular spasm the pulmonary rather than the bronchial vessels are affected. I have equally no doubt that in other cases the immediate mechanism of the paroxysm is dependent on irregular turgescence of the bronchial mucosa; and equally no doubt that in some cases turgescence of the bronchial mucosa is preceded, accompanied or succeeded by inflammatory or subinflammatory conditions, associated with exudation into the bronchioles. Again we find, as an underlying diathesis in some patients, gout or, if that term be preferred, lithemia; in others rheumatism. In some patients, but by no means all, nasal abnormalities exist. They may be causative or merely coincident; the most intractable case I have had was in a man from whom I removed a large nasal polyp and in whom, although the relief to nasal breathing was marked, the asthma persisted. In other cases abnormalities of the upper pharynx, of the lower pharynx, of the tongue, of the thyroid gland are found. In one case, referred to me by Dr. Weir Mitchell, there was tonic spasm of one vocal band apparently due to pressure by a hardened right apex upon the recurrent laryngeal nerve. In this case several nasal polypi had been removed by the late Dr. Harrison Allen without relief to the tendency to asthmatic paroxysms. Many patients subject to asthma are highly neurotic and some have hay-fever; the asthma occurring both in association with this latter syndrome and during times of freedom from nasal and ocular symptoms. In other cases there is associated with the tendency to paroxysmal dyspnea, a paroxysmal albuminuria; the latter occurring both during the period of respiratory distress and during the intervals of freedom, although in some instances they may seem to alternate.

In this outline I have not attempted to exhaust the list of associations, but merely to indicate the great variety of the conditions under which asthma may be manifested

as one of a group of symptoms, or even as the single prominent symptom of a general disorder.

Adrenal substance is not applicable to the treatment of all asthmatic patients or to all varieties of asthma. It is applicable in the treatment of some of those in whom this affection is associated with other manifestations of what I have elsewhere termed vasomotor ataxia,¹ of the relaxing variety. Under this head I include, among others, patients who are subject to urticaria or in whom factitious urticaria may be readily produced; those who are, vascularly, extremely sensitive to slight changes in weather and climate, or who exhibit peculiar idiosyncrasies in this respect, as in their reaction to drugs; those whose cardiovascular balance is easily disturbed by emotion or by digestive disorder or other slight intoxication; some hay-fever subjects; persons subject to congestive hemicrania; and those who show signs of renal leakage, either by intermittent albuminuria, or by the occasional presence of red blood-cells in the urine, without decided hematuria and without the persistent presence of tube casts; in whom, therefore, we are dealing with what may be termed functional rather than organic renal lesion. By the apparent paradox of "functional lesion," I do not mean to imply the absence of structural change—on the contrary, to indicate that there is a distinct structural—or perhaps it would be better to say "compositional"—abnormity, not sufficiently gross to be detected by our present methods of research. But this abnormity in the great class of patients herewith included is congenital and is thus, as it were, normal to the individual.

Whether it be metabolic or of other nature in ultimate analysis is a subject too recondite for present discussion. Biochemistry and biophysics are ~~neither~~ *not yet* sufficiently advanced to answer. Clinically, however, the fault is found in the vascular taxis.

¹ Am. Jour. Med. Sci., February, 1894.

Believing that in such cases the immediate mechanism of the obstruction to respiration, manifested by the asthmatic paroxysm, is an irregular swelling of the bronchial mucosa, allied to the condition of circumscribed edema—angioneurotic edema—or urticaria, and that by increasing the vascular tone through the administration of that substance which Nature seems to have designed for its maintenance, we might prevent such attacks, I have, during the last few years, used adrenal substance in the treatment of such patients. It has in but one dubious instance served to cut short a paroxysm, though it has occasionally mitigated distress in greater or less degree. It has, however, been useful in averting the recurrence of paroxysms and in finally bringing about a state of freedom from fear of their recurrence. I, therefore, speak of the use of adrenal substance not as “a treatment for asthma” but as a measure “applicable in the treatment of certain cases” of that affection. Physicians accustomed to exactitude in language will readily discern the difference between these methods of statement.

As illustrative both of the usefulness and of the limits of usefulness of this agent in the management of certain cases of asthma, the following case may be given in outline:

Miss X. Y. Z., aged 22 years, was first seen in consultation, at Atlantic City, in June, 1897. She was then confined to bed with constant dyspnea, aggravated in paroxysms, the paroxysms occurring at night and relieved after an hour or two of orthopnea by critical expectoration of large quantities of a thin watery fluid. During the day this expectoration would continue in less degree, but would cease during sleep. Sleep would be broken in on by the asthmatic paroxysm and return with the re-establishment of the discharge. Attacks of excessive rapidity of the heart and paroxysms of distressing sweating were also complained of. It was stated that this condition had followed an attack of influenza which

occurred during the preceding February, since which time the patient had not been out of bed. She was feeble, nervous and apparently anemie, but not hysterical. The temperature ranged between 99 and 100.5 F., irregularly. Physical examination gave hyperresonance of the upper portion of the right lung; normal resonance elsewhere, and diffuse mucous, sonorous and sibilant râles in all portions of the chest. The heart was feeble and rapid, rate 96. No murmur was heard. Preordial dulness was perhaps slightly enlarged. This was during a period of comparative quiescence, the respirations being shallow and slightly accelerated to 24 to the minute, and considerable subjective distress being complained of, but no asthmatic paroxysm being manifested. Dermographism was readily produced; the nails showed typical red crescents and were of a peculiar lemon tint not due to artificial coloring. The father of the patient was said to have died of asthma and tuberculosis, following pneumonia. At that time, eight years previously, the patient had suffered similarly to the present attack but not for so long a period. Examination of the patient's sputum for tubercle bacilli had not been made during either attack. The urine was free from albumin.

Apart from diet, the treatment tentatively advised was the injection of very small doses of hyosein hydrobromate with morphin and stryehnin at night, for at most three consecutive nights, and during the day the use of a mixture containing ammonium bromid. Iron preparations and syrup of hydriodic acid had been used without much good effect. Slight relief followed. The patient was brought to Philadelphia in July, where she was placed under the care of my friend Dr. Eshner, with whom I again saw her in consultation. Examination of the urine now showed the absence of albumin; examination of the sputum showed the absence of tubercle bacilli, and examination of the blood showed reduction of red

corpuscles to about 70 per cent. and hemoglobin to about 60 per cent. of normal.

The treatment proved to be most difficult. Apart from hygienic and general tonic treatment, many approved remedies were used without benefit. Some of the drugs that gave greater or less relief may be mentioned. Atropin checked sweating and expectoration temporarily, but the symptoms reappeared in greater degree on its withdrawal. Picrotoxin was employed on the theory that the paroxysms were due to vasomotor paresis with turgescence of the bronchial mucosa. This gave some relief, but recovery seemed still distant. Thymus gland substance gave better results, but asthmatic paroxysms still recurred. Albumin appeared in the urine. It was then determined to use adrenal substance. Burroughs & Wellcome's tablets, 5 grains each, were prescribed once daily, then twice, then three times daily, and finally the patient for a short time took 90 grains daily. A striking improvement shortly became manifest. The constant dyspnea first disappeared, then the paroxysmal nocturnal attacks became less frequent and less severe. Recovery was not rapid but was continuous.

In October the patient was able to go out of doors, and inhalations of compressed air with exhalations into rarefied air were then added to the treatment for its effect as a method of neuromuscular gymnastics, as also for direct effect on the blood-vessels at fault. The albuminuria noted was intermittent and disappeared after ten months. Since this time the patient has had no recurrence of symptoms similar to those of the original attack; though being allowed to go without medicine on account of the improved condition, there is at times recurrence of albuminuria, which quickly disappears under treatment with adrenal extract; and once there was a brief attack of dyspnea with asthmatic exacerbation, which likewise yielded quickly to treatment. While it is obvious that dependence in this case was not placed alone

on the adrenal substance, yet its marked effect in heightening the tone of the blood-vessels, in diminishing and finally checking the peculiar expectoration, and its similar effect on the night sweats, favor the belief that it was an active agent in the control of the asthmatic symptoms. The tachycardial paroxysms had ceased before it was administered—under the influence of rest, medication, and allaying of fear.

In other patients the result has been about the same as that already narrated. Hyoscin, morphin and strychnin have been given for immediate control of paroxysms, sometimes aspidospermin or other appropriate remedy for the quick relief of dyspnea, and adrenal extract for control of the underlying condition.

It would be wearisome, as well as useless, to detail histories. Apart from so-called hay-asthma—which is another story and belongs to another speaker—success has been reached only in those cases, about twelve in the course of a little more than two years, in which from the crescentic markings on the nails, from the tendency of the hands to excessive color changes, or to sweating on slight temperature variations, from the facility with which dermographism or factitious urticaria could be produced, from the enlargement of the thyroid gland, from the tendency to cardiac palpitation, or even tachycardia, or from the occurrence of other vasomotor crises, such as migraine or angioneurotic edema or nervous vomiting, or if necessary from the *experimentum crucis* of increased distress on inhalation of amyl nitrite—one could recognize the tendency of the subject to loss of control of vascular tone on slight provocation. In one case the paroxysm of asthma—or perhaps of obstructive dyspnea—was preceded by angioneurotic swelling of the tongue, and when this was reduced by the prompt local application of suprarenal extract, the paroxysm was averted or modified in severity. It was interesting to note that in this case the swelling of the tongue was not

always followed by dyspnea, but sometimes by a gastric crisis, of pain, or less frequently, vomiting of a thin, tasteless fluid. I never saw these attacks, and, therefore, rely entirely on the description of the patient and her physician. The circumscribed swelling of the tongue I saw in my office, but it was promptly reduced by suprarenal substance locally, and no other manifestation followed.

I believe that we have in this substance a decided addition to therapeutic resources; quite active when used locally, and hence to be remembered in the prompt treatment of urticaria or edema of the upper air-passages—and less active, but still definitely useful by internal administration in controlling urticaria or circumscribed edema or similar condition affecting the bronchial mucosa.

It is not a specific for asthma. It is without good influence, perhaps capable of bad influence, on cases that are really spasmodic; that is, due to contraction of the bronchial muscles. But it is of definite use in that perhaps smaller number of cases of asthma in which, as I have indicated, the paroxysm is but one other manifestation of a congenital fault of structure or of metabolism, affecting the vasomotor system and thus permitting the cardiovascular balance, and especially the tonicity of the blood-vessels, to be readily overturned by exciting causes that would have but slight, if any, effect on other individuals. In such cases a more or less continuous administration of adrenal substance, in sufficient quantity to maintain the vascular tone, will act as a preventive, enabling the reactive forces of the individual to combat more successfully the toxins of internal and external origin, the emotional, meteorologic, thermal, and climatic influences, and other sources of disturbance that ordinarily provoke the paroxysm.

As to its dosage, the rule is that of Professor Eilerslie Wallace for bleeding in puerperal eclampsia—"Enough."


There is great difference in cases and in individuals: Beginning with small doses frequently repeated, e. g., 1 grain every hour or every two hours, or with a moderate dose, say 5 grains, once or twice daily, we learn the tolerance of the individual, the tractability or intractability of the symptoms, and regulate accordingly. I have given as few as 3 and as many as 90 grains of the desiccated gland substance in the twenty-four hours. Five or 10 grains every second or third hour during waking hours is a fair dose. In some cases, however, the unnecessary animal substances retained in the preparation give rise to diarrhea with offensive discharges. If we could have the active agent alone our therapy would be much more definite.

What the active agent is, and how much or how little of that active agent is absorbed, I must leave to laboratory students to determine. Clinically I have watched closely and critically enough to satisfy myself that neither the susceptibility of patients to suggestion, nor the activity of the observer's imagination are sufficient ~~in themselves~~ to account for the whole of the results.






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